UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,261	05/10/2001	Geoffrey Goldspink	117-351	5457

23117 7590 07/02/2003

NIXON & VANDERHYE, PC
1100 N GLEBE ROAD
8TH FLOOR
ARLINGTON, VA 22201-4714

EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	18

DATE MAILED: 07/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/852,261	GOLDSPINK ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover she t with th correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14 16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Amendments filed 20 May 2003 (Paper No. 15) and 20 May 2003 (Paper No. 17) have been received and entered in full. Claims 1-13 have been cancelled and 14-56 have been added.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections and/or Rejections

3. The objection to the Specification as set forth at ¶5-6 pp. 4 in the previous Office Action (Paper No. 13, 20 November 2002) is withdrawn in view of Applicant's amendments (Paper No. 17, 20 May 2003).

4. The rejection of claims **1-6** and **9-11** under 35 U.S.C. §112 ¶1 as set forth at ¶7-14 pp. 5-9 in the previous Office Action (Paper No. 13, 20 November 2002) is *moot* in view of Applicant's cancellation of said claims (Paper No. 17, 20 May 2003).

5. The rejection of claims **1-6** and **9-11** under 35 U.S.C. §112 ¶1 as set forth at ¶7-14 pp. 5-9 in the previous Office Action (Paper No. 13, 20 November 2002) is *moot* in view of Applicant's cancellation of said claims (Paper No. 17, 20 May 2003). It is noted that claims 14-56 were presently added and in form and substance represent a new presentation of the invention as claimed in the cancelled claims 1-6 and 9-11 the rejection is here maintained *in part*.

Maintained Objections and/or Rejections

6. Claims **14-56** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a method of treating a damaged **peripheral nerve** said treatment comprising administering to a subject comprising said nerve an effective non-toxic amount of an MGF (mechano-growth factor) polypeptide, said administration comprising delivering said MGF polypeptide to the side of said damage, said MGF polypeptide comprising at least one sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, and SEQ ID NO: 6 wherein the MGF polypeptide is administered to said subject at a site of said damaged nerve bye means of a conduit placed around the damaged nerve,* does not reasonably provide enablement for *treatment of **central nervous** system damage, amino acid sequences having 80% or greater sequence identity to SEQ ID NO: 2, 4, or 6, an amino acid sequence encoded by a nucleic acid sequence capable of selectively hybridizing to a nucleic acid sequence encoding SEQ ID NO: 2, 4, or 6, or an amino acid sequence comprising a fragment of at least 20 contiguous amino acids of any SEQ ID NO: as claimed.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims as set forth at ¶7-14 pp. 5-9 in the previous Office Action (Paper No. 13, 20 November 2002).

7. The Applicant traverses the rejection of claims **1-6** and **9-11** (the rejection now be applied to presently added claims **14-56**) on the following grounds: **(a)** the Specification details the use of MGF polypeptide to reduce motorneuron loss in nerve injury (citing pp. 5, 36, Example 1, Example 2), **(b)** MGF has beneficial properties for damaged nerves in general and is capable of stimulating re-growth of neurons, **(c)** Vejsada *et al.* (1998) "Synergistic but Transit Rescue Effect of BDNF and GDNF of Axotomized Neonatal Motoneurons." Neuroscience **84**(1): 129-

139, Vejsada *et al.* (1995) "Quantitative Comparison of the Transient Rescue Effects of Neurotrophic Factors on Axotomized Motoneurons In Vivo." European Journal of Neuroscience 7: 108-115, and EP 0308 386 do not discuss MGF, **(d)** the variants and derivatives of MGF are clearly claimed and structural requirements are recited, **(e)** no unreasonable degree of experimentation would be necessary to make and use MGF polypeptides as claimed, **(f)** the Applicant is not required to provide "all the applicable homologues", **(g)** the prior art offers support for the claims, and **(h)** based on the Examples and guidance provided in the Specification, no obstacles exist to the application of the polypeptide in a therapy using a conduit. The Applicant's arguments have been taken into consideration and are not found persuasive for the following reasons.

8. The instant claims are drawn very broadly to methods treating nerve damage, even served nerves, in both the peripheral nervous system and central nervous system. Since the specification fails to provide any guidance for the successful central nervous system treatment, administration of MGF polypeptides, and since resolution of the various complications in regards treating nerve damage, especially central nervous system nerve damage is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations of MGF polypeptides and assessment of the therapies. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

9. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of using MGF polypeptides to treat nerve damage. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a specific polypeptides *in vivo* based solely on its performance of the plasmid encoding them as *gene therapy agents* is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo* treatments, such a disclosure would not be considered enabling since the state of nerve damage treatment is highly unpredictable. Therefore the Specification does not present adequate written description of the instant invention to allow a skilled artisan to practice the invention to the full scope of the claims as written. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

10. Concerning "**(a)**", the Specification clearly demonstrates the use of SEQ ID NO 1, 3, and 5 as cDNA's in a gene therapy regiment for peripheral nerve damage. While the merits of the use of SEQ ID NO: 1, 3, and 5 as cDNA's in gene therapy are detailed, it is not within the scope of the claims as written. The instant claims are drawn to the use of SEQ ID NO: 2, 4, and 6 the polypeptides encoded by SEQ ID NO: 1, 3, and 5 in direct administration of said polypeptides.

Therefore the Specification does not present adequate written description of the instant invention to allow a skilled artisan to practice the invention.

11. In view of the Applicant's arguments "**(b)**", the Examiner *accepts* that MGF exhibits some salubrious action for nerves, as shown by the Applicant's disclosure. However, the Examiner puts forth the rejection in terms of scope, as the prior art teaches nerve damage can be divided into two categories: (A) peripheral nervous system and (B) central nervous system. This separation is well known in the art and is based upon anatomical, cellular, and molecular differences between the two branches of the mammalian nervous system. While peripheral nerve damage is treatable and is accepted in the art to respond to treatments including growth factor based regimes, central nervous system damage, especially severed nerves of the central nervous system are not known to be rejoinable through medical technology [see Jackowski "Neural injury repair: hope for the future as barriers to effective CNS regeneration become clearer." British Journal of Neurosurgery **9**: 303-317].

12. Concerning Applicant's questions of the references listed in "**(c)**", the Examiner *accepts* the Applicant's arguments that none of the three references discuss MGF as claimed and are provided as background information on treating nerve damage.

13. Regarding derivatives and fragments of *SEQ ID NO: 2, 4, and 6* as well as polypeptides encoded by derivatives and fragments of *SEQ ID NO: 1, 3, and 5* as presented in "**(d)**", the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with

a reasonable expectation of success are limited. For instance, Hameed *et al.* "Expression of IGF-I splice variants in young and old human skeletal muscle after high resistance exercise." The Journal of Physiology **547**(Pt. 1): 247-254 teaches that MGF is a splice variant of IGF. Therefore, alterations in the sequence of MGF could represent a different form of IGF, one that may not necessarily hold the same properties required by the claims (Figure 1; pp. 251). More importantly, certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize

that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

14. On "**(e)**", the Examiner *accepts* the Applicant's arguments that MGF as encoded by SEQ ID NO: 1, 3, and/or 5 is readily practiced. However, as discussed above, mutations, fragments,

and sequence homology variants have their own inherent problems. In addition, as discussed herein, the Specification does not provide any evidence that the administration of the polypeptides as claimed. Also, the breadth of the claims bring unpredictability to practicing the instant claims to their full scope.

15. In regards to "**(f)**", the Examiner, as discussed above, maintains that mutations, fragments, and sequence homology variants have their own inherent problems. In addition, as discussed herein, the Specification does not provide any evidence that the administration of the polypeptides as claimed. Also, the breadth of the claims bring unpredictability to practicing the instant claims to their full scope. Thus, while the Applicant is not required per se to provide "all the applicable homogues" of MGF the Specification provides only prophetic guidance to practicing the invention to the full scope of the claims.

16. On the prior art "**(g)**", the upregulation of MGF following exercise is well documented. However, this is not relevant to the instant application. The instant claims are drawn to the treatment of nerve damage with MGF polypeptides, a subject with which the prior art is silent.

17. Finally concerning "obstacles" to the instant invention as argued in "**(h)**", the Examiner *accepts* that a physician may readily deliver a polypeptide to a particular site of injury. However, this is not a point of contention. The scope of enablement hinges on the treatment of central versus peripheral nerve damage and the use of variants and derivatives of SEQ ID NO: 2, 4, and 6. As taught by Goldspink and Yang (December 2001) "Effects of Activity on Growth Factor Expression." International Journal of Sport Nutrition and Exercise Metabolism **11**: S21-S27 teaches that mutations in IGF-I can alter muscle mass and anabolic processes frquir3ed for cell repair and preventing cell death, it is noted that MGF is a splice variant of IGF and thus meeting

the limitations of the sequence variation (pp. S25). Furthermore, Goldspink and Yang (2001) describe the MGF polypeptide as "unstable" and degrading rapidly during purification attempts (pp. S24). Taken together, these obstacles are not adequately addressed by the instant Specification.

18. The rejection of claims **14-56** under 35 U.S.C. §112 ¶1 is hereby maintained.

Summary

19. Claims **14-56** are hereby rejected.

20. The following art was found by the Examiner during the art search for the instant application and is here made of note:

a. US 6221842 B1 (24 April 2001) Goldspink

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
June 20, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER